UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	NG DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,675	2/28/2002	Samuel Weiss	032901-044	2536

21839 7590 09/05/2003

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	10/084,675	WEISS ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *11-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-22* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-10) drawn to a method of increasing stem cell number in Paper No. 9 (18 June 2003) is acknowledged. The traversal is on the ground(s) that Groups III to VIII should be rejoined because they represent members of a Markush Group. This is not found persuasive because Applicant has elected Group I therefore arguments on rejoinder of Groups III through VIII are not relevant. Concerning Groups III to VIII, these groups are independent and distinct as each is drawn to a different disease/condition with a distinct and non-overlapping patient population as well as different biological mechanisms thus they are not a true Markush Group. Therefore, each disease requires separate and non-overlapping search and consideration. Claims 11-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9 (18 June 2003). The requirement is still deemed proper and is therefore made FINAL.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: it does not claim priority under 35 U.S.C. §119(e) to U.S. Provisional Application Serial No. 60/272940 (2 March 2001).

Obvious-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims **1-8** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/084671 (herein cited as U.S. Patent Application Publication US 2002/0165213 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-8 of Application No. 10/084671 recite the same limitations as instant claims 1-8, except differing in scope. The claims 1-8 of Application No. 10/084671 are limited to estrogen while instant claim 1 is the broader genus of "ovarian hormone" with estrogen as a further limitation of instant claim 1 in dependent claim 8. Thus not only does the genus "ovarian hormone" encompass estrogen as a species (see the instant Specification pp. 21 for a definition), instant claim 8 specifically recites estrogen. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims **1 and 7-10** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *increasing neural stem cell number in vitro comprising providing an effective amount of an ovarian hormone to at least one neural stem cell under conditions which result in an increase in the number of neural stem cells*, does not reasonably provide enablement for *practicing said method in vivo or in a patient*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. The claims are drawn very broadly to methods of increasing neural stem cell numbers via administration of an ovarian hormone. The language of said claims encompasses both *in vivo* and *in vitro* uses in any animal using any ovarian hormone or functional analog thereof.

6. The specification teaches that pregnant female mice show approximately 40% more neural stem cells than virgin mice in the subventricular zone (SVZ). Also, ovarectomized mice show a 36% reduction in neural stem cells in the subventricular zone (SVZ). Finally, neural stem cell cultures (*in vitro*) incubated with a combination of EGF and an ovarian hormone showed more neural stem cell growth that with EGF alone (pp. 15-17).

7. The specification fails to provide any guidance for the successful increase in neural stem cell number *in vivo* through administration or otherwise providing an ovarian hormone, and since

resolution of the various complications in regards to targeting the role a hormone in stimulating neurogenesis or neural stem cell growth *in vivo* is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations, dosages, and administration regiments with known ovarian hormones and functional analogs to correlate with an increase in neural stem cells in the subject. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a hormone based solely on extirpation experiments as highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo*, such a disclosure would not be considered enabling since the state of ovarian hormones and neural stem cells is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) **The breadth of the claims;**
(B) **The nature of the invention;**
(C) **The state of the prior art;**
(D) **The level of one of ordinary skill;**
(E) **The level of predictability in the art;**
(F) **The amount of direction provided by the inventor;**
(G) **The existence of working examples; and**
(H) **The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

9. The following references are cited herein to illustrate the state of the art of ovarian hormones and neural stem cells.

10. On the nature of the invention, Kang *et al.* (November 2001) "Effects and Neuro-toxic Mechanisms of 2, 2', 4, 4', 5, 5'-Hexachlorobiphynyl and Endosulfan in Neuronal Stem Cells." Toxicology **63**(11): 1183-1190 teaches that biochemical compounds known as endocrine disrupters are exogenous compounds that mimic the action of estrogen or other hormones and influence endocrine activity in mammals. Endocrine disruptors that mimic estrogen affect the central nervous system as well as the reproductive tract (pp. 1183, 1186). Thus due to the breath of the claims, which encompass a wide range of compounds that may act as ovarian hormones, as outlined in the instant Specification (pp. 21), the skilled artisan is confronted with a undue burden of experimentation to first identify "ovarian hormones" that are suitable for administration to animals and then to determine which "ovarian hormones" satisfy the claims.

11. On the breadth of the claims, Goldman (August 1998) "Adult Neurogenesis: From Canaries to the Clinic." J. Neurobiol. **36**(2): 267-286 teach that estrogen is responsible for seasonal neurogenesis in songbirds. Schlinger and Arnold (May 1991) "Brain is the major site of estrogen synthesis in a male songbird." PNAS **88**: 4191-4194 teaches that estrogen is produced in the brain of both male and female songbirds. Thus the skilled artisan is confronted with an example of where the method itself is already found in nature, thus adding a level of complication to successful practice. Furthermore Grisham and Arnold (1994) "A Direct Comparison of the Masculinizing Effect of Testosterone, Androstenedione, Estrogen, and Progesterone on the Development of the Zebra Finch Song System." Journal of Neurobiology **26**(2): 163-170 teach that administration of estrogen and progesterone differ in their effects on

the growth and development of neurons in the central nervous system (Figure 1-5). Thus requiring of the skilled artisan a series of trial and error experiments to determine which ovarian hormone increases neural stem cell numbers.

12. On the prior art, Mathews and Arnold (December 1991) "Tamoxifen's Effects on the Zebra Finch Song System are Estrogenic, not Antiestrogenic." Journal of Neurobiology **22**(9): 957-969 teach that the effects of tamoxifen, an estrogen analog, depend on if it is administered alone, in combination with an estrogen such as estradiol (pp. 958). Thus the skilled artisan is confronted with an unpredictable system where tamoxifen's effects are conditionally based.

13. On working examples, Shingo *et al.* (3 January 2003) "Pregnancy-Stimulated Neurogenesis in the Adult Female Forebrain Mediated by Prolactin." Science **299**: 117-120 represents a post-filing reduction to practice of the invention as claimed, wherein pregnant mice showed increased neurogenesis versus virgin mice (pp. 117). Shingo *et al.* sought to differentiate between the different hormones active in pregnancy that may contribute to this neurogenesis in the subventricular zone (SVZ) and the olfactory bulb. Shingo *et al.* found:

> To explore the underlying mechanism, we first tested whether estrogen or progesterone, administered alone or together, could mimic the increase in neurogenesis seen in either pregnant or pseudopregnant mice. Whether infused directly into the brain or peripherally to normal or ovariectomized females, estrogen and/or progesterone failed to increase the numbers of BrdU-immunoreactive cells in the SVZ (Table S1). Taken together, these data suggest that although circulating maternal hormones are likely responsible for the pregnancy- and pseudopregnancy-induced increases in forebrain SVZ neurogenesis, estrogen and/or progesterone are not candidates for mediating this response.

Further, Shingo *et al.* demonstrated that prolactin is the most likely candidate for the neurogenesis seen in pregnant and pseudopregnant mice (Figures 1-3).

14. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments and poorly correlated extirpation experiments to the administration of an ovarian hormone to increase the number of neural stem cells *in vivo* as exemplified in the references herein.

15. Claims **2-6** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons discussed above (see ¶4-14 in this Office Action).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims **1, 7, 8, 9,** and **10** are rejected under 35 U.S.C. 102(b) as being anticipated by US 5824489 (20 October 1998) Anderson *et al.* US 5824489 teaches a culture medium containing 20 nM progesterone for growing rat neural crest stem cells thus meeting the limitations of claims 1, 7, and 9 (Example 2). It is noted that US 5824489 uses GIBCO DMEM media which contains phenol red, an "estrogen" according to the instant Specification thus meeting the limitations of claims 8 and 10 (pp. 9 line 21; also DMEM Media Formulation attached).

17. Claims **1, 7, 8, 9,** and **10** are rejected under 35 U.S.C. 102(e) as being anticipated by US 2002/0064873 A1 (30 May 2002) Yang & Johe. US 2002/0064873 teaches a culture medium containing 100 mg/L progesterone for growing mammalian, specifically rat and human, neural stem cells thus meeting the limitations of claims 1, 7, and 9 ([0059]). US 2002/0064873 also teaches the addition of a mitogen, a substance which enhances or causes cell growth, including but not limited to β-estadiol thus meeting the limitations of claims 1, 7, and 9 ([0097]; claims 1 and 3). It is noted that US 2002/0064873 also teaches the growth of rat and human CNS stem cells in the progesterone medium with and without the addition of β-estadiol thus meeting the limitations of claims 1, 7, 8, 9, and 10 (claims 1 and 3). It is noted that US 5824489 uses GIBCO DMEM media which contains phenol red, an "estrogen" according to the instant Specification thus meeting the limitations of claims 8 and 10 (pp. 9 line 21; also DMEM Media Formulation attached).

Summary

18. Claims **1-10** are hereby rejected.

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

a. US 6103530 (15 August 2000) Carpenter

b. US 5851832 (22 December 1998) Weiss *et al.*

c. US 5843934 (1 December 1998) Simpkins

d. US 2003/0049838 A1 (13 March 2003) Thompson *et al.*

e. US 2003/0054998 A1 (20 March 2003) Shingo *et al.*'

f. WO 03/024472 A2 (27 March 2003) Weiss *et al.*

g. Weiss *et al.* (1 December 1996) "Multipotent CNS Stem Cells are Present in the Adult Mammalian Spinal Cord and Ventricular Neuroaxis." The Journal of Neuroscience **16**(23): 7599-7609

h. Nordeen *et al.* (1987) "Sexual Differentiation of Androgen Accumulation Within the Zebra Finch Brain Through Selective Cell Loss and Addition." The Journal of Comparative Neurology **259**(3): 393-399

i. Inestrosa *et al.* (1998) "Cellular and Molecular Basis of Estrogen's Neuroprotection." Molecular Neurobiology **17**(3): 73-86

j. Kawas *et al.* (1997) "A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease." Neurology **48**(6): 1517-1521

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
August 28, 2003